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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,790	MEYERS ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 11-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 10* is/are rejected.

7)☒ Claim(s) *9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8,11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group VIII (claims 9 and 10, molecule 32374) in Paper No. 13 is acknowledged. A telephone phone call to Carolyn Favorito on January 13, 2003, clarified that molecule 32374 is represented by polynucleotides with SEQ ID NO: 1 and 3 and a polypeptide with SEQ ID NO: 2. Claims 9 and 10 will be examined to the extent that they read on SEQ ID NOs 1-3.

2. Claims 1-8 and 11-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 13.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

4. The information disclosure statement filed on February 25, 2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because references 1-16 disclose actions taken by applicants (searching of a database), therefore these are not proper references. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of

filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

5. The information disclosure statement filed on October 7, 2002 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because references 5-7 disclose actions taken by applicants in accessing the database, but not the results of such actions. It has been placed in the application file, but the information referred to therein has not been considered as to the merits (for references 5-7). Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

6. The information disclosure statement filed on October 7, 2002 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. The reference which has not been considered is reference number 1, a WO publication number 98/49276 A, in Japanese.

Specification

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

Numerous hyperlinks are present on pages 6-12, 14, 21 and 25.

8. The disclosure is objected to because of the following informalities: no ATCC accession numbers are given for the clones listed on pages 3, 4, 21, 32, 33, 36-42.

Appropriate correction is required. No new matter should be introduced.

9. The specification contains numerous references to ATCC deposits, but without deposit numbers. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See C.F.R. 1.808.

If a deposit is not made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposit will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposit will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 CRF 1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

Drawings

10. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following figures not mentioned in the description: Figure 1C is not described in the Brief Description of Drawings on page 6, line 2. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

11. Claims 9 and 10 are objected to as being dependent from a non-elected claim 4, drawn to a polypeptide which is used in the methods of claims 9 and 10. Appropriate correction is required.

12. Claims 9 and 10 objected to because of the missing ATCC accession numbers in lines 7, 10 and 16 of claim 4. Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 9 is indefinite over the recitation of "the polypeptide" in lines 5 and 6. It is not clear what polypeptide this term refers to, since lines 1 and 2 contain a limitation "a polypeptide" and lines 2 and 3 contain limitations "the polypeptide of claim 4" and "a polypeptide of claim 4", respectively.

15. Before proceeding with the 35 USC § 112, first paragraph rejections, the facts and assertions presented by Applicants in the specification will be summarized, so that they do not need to be repeated for each of the rejections.

Facts and Assertions Presented by Applicants Regarding 32374 Polypeptides

A) Claims under consideration. For the purpose of utility rejection only the part of claim 9 drawn to a polypeptide of claim 4 will be considered. Claim 9 is drawn to a method for identifying a compound which modulates the activity of a polypeptide of claim 4, the method comprising contacting a cell expressing the polypeptide of claim 4 with a test compound and determining the effect of the compound on the activity of the polypeptide. Claim 10 is drawn to a method of modulating the activity of a polypeptide of claim 4 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide. Therefore, utility of methods of claims 9 and 10 depends on whether the polypeptide has an established activity which can be monitored during the course of modulation with a given compound.

The polypeptide of claim 4 is an isolated polypeptide (referred to as a 32374 polypeptide) selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof,

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof under stringent conditions,

c) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2, and

d) the amino acid sequence of SEQ ID NO: 2.

B) Facts presented by Applicants in the specification. The following facts were presented by Applicants regarding a polypeptide with amino acid of SEQ ID NO: 2, which is encoded by polynucleotides with SEQ ID NO: 1 (full sequence) and SEQ ID NO: 3 (cDNA):

a) SEQ ID NO: 1 has 2893 base pairs (bp), SEQ ID NO: 3 has 1041 bp and SEQ ID NO: 2 has 346 amino acids. SEQ ID NO: 3 (cDNA) overlaps with SEQ ID NO: 1 from bp 274-1314 of SEQ ID NO: 1 (see Figures 1A-1C).

b) Tissue distribution of 32374-like sequences was measured using a Taq-Man RT-PCR assay, and the highest expression was found in the brain cortex (Example 3, Tables 1, 2). In rat tissue the highest expression was found in the adrenal gland.

c) No expression of polypeptide with SEQ ID NO: 2 was shown from either SEQ ID NO: 1 or SEQ ID NO: 3. Examples 4 and 5 describe theoretical procedures for expressing the polypeptide in bacterial or COS cells.

d) Figure 2 shows a hydropathy plot of the predicted amino acid sequence of SEQ ID NO: 2. The following fragments of the polypeptide were delineated based on this plot: hydrophobic sequences with amino acids 28-38, 160-170, 290-305 (and their fragments), hydrophilic sequences with amino acids 5-13, 245-255, 320-330 (and their fragments), a sequence which includes a cysteine or a glycosylation site.

e) Figures 3-12 show alignments of various parts of SEQ ID NO: 2 with different consensus sequences derived from a variety of databases.

f) The predicted protein structure contains the following structural features:

- one protein kinase domain (PFAM Accession number PF00069) located at about amino acids 1-231 of SEQ ID NO: 2; additional determination of the kinase domain presence can be made by searching a SMART database (page 14, lines 15-26); the protein kinase domain may be also located by searching a PFAM database or ProDom database (page 23, lines 10-31; page24, lines 1-3); the following alignments were made:

i) amino acids of 32374 kinase domain (226-285 and 321-346) were aligned with consensus amino acid sequences SEQ ID NO: 8 and 9 of the ProDom family PD193106, and amino acids 226-285 were found to be 95% identical to SEQ ID NO: 8 and amino acids 321-346 were 100% identical to SEQ ID NO: 9 (page 24, lines 4-11);

ii) amino acids of human 32374 kinase domain (166-245) were aligned with consensus amino acid sequences SEQ ID NO: 10 of the ProDom family PD057870, and amino acids 166-245 were found to be 30% identical to SEQ ID NO: 10 (page 24, lines 12-18);

iii) amino acids of human 32374 kinase domain (30-189) were aligned with consensus amino acid sequences SEQ ID NO: 15 of the ProDom family PD156063, and amino acids 30-189 were found to be 22% identical to SEQ ID NO: 15 (page 24, lines 19-25);

iv) amino acids of human 32374 kinase domain (29-262) were aligned with consensus amino acid sequences SEQ ID NO: 16 of the ProDom family PD325057, and amino acids 29-262 were found to be 26% identical to SEQ ID NO: 16 (page 24, lines 26-30 and page 27, lines 1, 2);

- one N-glycosylation site (PS00001) located at about amino acids 7-10 of SEQ ID NO : 2,
- one Glycosaminoglycan attachment site (PS00002) located at about amino acids 281-284 of SEQ ID NO : 2,
- three camp- and cGMP-dependent protein kinase phosphorylation sites (PS00004) located at about amino acids 128-131, 204-207 and 245-248 of SEQ ID NO : 2,
- three protein kinase C phosphorylation sites (PS00005) located at about amino acids 72-74, 120-122 and 248-250 of SEQ ID NO : 2,
- four casein kinase II phosphorylation sites (PS00006) located at about amino acids 137-140, 154-157, 179-182 and 340-343 of SEQ ID NO : 2,
- one serine/threonine protein kinases active-site signature (PS00108) located at about amino acids 92-104 of SEQ ID NO : 2 (page 13, lines 15-31; page 14, lines1-14),
- the polypeptide may include at least one transmembrane domain, which can be identified on the basis of the hydropathy plot (amino acid residues 158-175 and 291-311 of SEQ ID NO: 2) or by analysis using transmembrane prediction methods (page 14, lines 28-31; page 15, lines 1-19),
- the polypeptide may include at least one non-transmembrane region, for example, amino acids 1-157, 176-290 and 312-346 of SEQ ID NO: 2 (page 15, lines 20-31; page 16, lines 1-3),
- the polypeptide may have an N-terminal cytoplasmic domain, for example, amino acids 1-157 of SEQ ID NO: 2 (page 16, lines 4-8),
- the polypeptide may have a C-terminal cytoplasmic domain, for example, amino acids 312-346 of SEQ ID NO: 2 (page 16, lines 9-22),

- the polypeptide may include a non-cytoplasmic loop, for example, amino acids 176-290 of SEQ ID NO: 2.

C) Assertions regarding protein function. On the basis of sequence comparisons, the following assertions are presented in the specification regarding function of the 32374 proteins:

a) The 32374 proteins contain a significant number of structural elements in common with members of the protein kinase family, the term "protein kinase" being defined as a protein or polypeptide capable of playing a role in signaling pathways associated with cellular growth. The 32374 proteins may be involved in regulation of transmission of signals from cellular receptors, modulation of entry of cells into mitosis, modulation of cellular differentiation, modulation of cell death, regulation of cytoskeleton function (page 21, lines 19-31; page 22, lines 1-6). The 32374 polypeptide is similar to known Ser/Thr kinases, therefore it is expected to be a kinase and function in phosphorylation of protein substrates (page 26, lines 22-27).

b) The 32374 proteins can be identified on the basis of at least one Ser/Thr kinase site, which includes the consensus amino acid sequence of SEQ ID NO: 37 and they have a 32374 activity (page 25, lines 20-30; page 26, lines 1-14). Applicants did not show that this consensus amino acid sequence is present in the polypeptide with SEQ ID NO: 2. A "32374 activity" refers to "... an activity exerted by a 32374 ... protein, polypeptide or nucleic acid molecule e.g., a 32374- ... responsive cell or on a 32374 ... substrate, e.g., a lipid or protein substrate, as determined in vivo or in vitro. As the 32374 ... polypeptides of the invention may modulate 32374- ... mediated activities, they may be useful for developing novel diagnostic and therapeutic agents for 32374- ... mediated or related disorders..." (page 27, lines 3-10).

c) Alterations in the activity of protein kinases may lead to growth-related disorders (page 22, lines 7-13), regulation of metabolism or pain disorders (page 22, lines 14-21), or brain disorders (page 27, lines 11-13). The list of possible disorders mediated by the 32374 proteins extends on pages 27, lines 14-30, pages 28, 29, page 30, lines 1-21.

d) The polypeptide may be used, for example, to generate antibodies (page 45, lines 30, 31; page 42, line 1; page 50, lines 24-30; page 51, 52), fusion proteins (page 47, lines 28-31; page 48), to treat disorders characterized by insufficient or excessive production of 32374 protein or its substrate or inhibitors (page 58, lines 26-31), to evaluate compounds for their ability to bind to the 32374 polypeptides (page 59, lines 7-15), in screening assays for candidate compounds (page 59, lines 18-31; page 60-67). The molecules can be used as surrogate markers for unspecified disorders (page 82, lines 5-31; page 83; page 84, lines 1-6).

D) Summary of facts and assertions provided by the Applicants: The protein with predicted amino acid sequence of SEQ ID NO: 2 is expected to be a kinase based on sequence homologies with other protein kinases, and should have at least one Ser/Thr kinase site (not identified for SEQ ID NO: 2). The protein exhibits unidentified "32374 activity", modulates unidentified 32374-mediated activities and is involved in unidentified 32374-mediated or related disorders. The protein has several putative structural features, including a kinase domain. The protein was not expressed from it's cDNA. The protein has no experimentally confirmed kinase or other activity, and no known substrate. The protein has not been linked to any specific disease.

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Utility

17. The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

18. Claims 9 and 10 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility.

The arguments regarding utility of the polypeptide of claim 4 will be presented first for the polypeptide of SEQ ID NO: 2 (part d of claim 4), then the rest of claim 4 (parts a-c) will be

considered. The claimed polypeptide compound (SEQ ID NO: 2) is not supported by a specific utility because some of the disclosed uses of the protein are not specific and are generally applicable to a wide variety of proteins (see Facts, C), part d). These are non-specific uses that are applicable to proteins in general and not particular or specific to the protein being claimed.

The polypeptide with SEQ ID NO: 2 does not have a substantial utility, since the assertions about it's structure and functions are not sufficient to determine that this polypeptide is indeed a protein kinase, and are not sufficient to establish the substrate upon which the polypeptide acts or a signaling pathway in which it is involved. Therefore Applicants' assertions about structure and function of the protein would need to be further investigated in order to confirm them.

It is noted that Applicants have listed sequences which are known in the databases as having a sequence similarity to a claimed sequence (see B), part f). Applicants assert that a kinase domain is present in the polypeptide and that it is similar to known Ser/Thr kinases, but it is not clear from the facts presented by Applicants that the sequences with which comparisons were made belong to proteins with known Ser/Thr kinase function. Sequence comparisons of the putative kinase domain of the polypeptide with SEQ ID NO: 2 with kinase domains from the ProDom database suffer from the following deficiencies:

1) comparison with ProDom consensus sequence of SEQ ID NO: 8 (not known to be a functional kinase domain) was performed for amino acids 226-285 of SEQ ID NO: 2 (60 amino acid fragment), even though on page 14 Applicants assert that the kinase domain of the polypeptide with SEQ ID NO: 2 extends from amino acid 1 to about 231;

2) comparison with ProDom consensus sequence of SEQ ID NO: 9 (not known to be a functional kinase domain) was performed for amino acids 321-346 of SEQ ID NO: 2 (26 amino

acid fragment), even though on page 14 Applicants assert that the kinase domain of the polypeptide with SEQ ID NO: 2 extends from amino acid 1 to about 231;

3) comparison with ProDom consensus sequence of SEQ ID NO: 10 (not known to be a functional kinase domain) was performed for amino acids 166-245 of SEQ ID NO: 2 (80 amino acid fragment), and there was only 30% identity over the 80 amino acids in this case;

4) comparison with ProDom consensus sequence of SEQ ID NO: 15 (not known to be a functional kinase domain) was performed for amino acids 30-189 of SEQ ID NO: 2 (160 amino acid fragment), and there was only 22% identity over the 160 amino acids in this case;

5) comparison with ProDom consensus sequence of SEQ ID NO: 16 (not known to be a functional kinase domain) was performed for amino acids 29-262 of SEQ ID NO: 2 (234 amino acid fragment), and there was only 26% identity over the 234 amino acids in this case, with amino acids 232-262 of SEQ ID NO: 2 outside of previously defined kinase domain.

Therefore sequence comparisons presented by Applicants do not convincingly show a presence of potentially functional kinase domain in the polypeptide of SEQ ID NO: 2.

The family of protein kinases is very large, with five major subfamilies, one of which consists of Ser/Thr kinases. The Ser/Thr family is very diverse, with distinct subfamilies, but there are also proteins with Ser/Thr kinase activity which are not related in sequence to any of the subfamily members (Hunter, Methods in Enzymology, vol. 200, pp. 3-37, 1991), pages 3 and 4. The kinases also have different regulators, such as cAMP, calmodulin or diacylglycerol (Hunter, page 5, second paragraph). Hanks et al. (FASEB J., vol. 9, pp. 576-596, 1995) investigated sequence conservation of kinase catalytic domains in 60 known protein kinases from all families. The kinase domains were further subdivided into 12 subdomains. Twelve kinase domain residues were found to be conserved in 95% of 370 kinase sequences, and subdomains VI, VIII and IX are

well conserved among the members of different families (page 576, 577, 587, 588). Applicants did not show that polypeptide of SEQ ID NO: 2 possesses any of the features described by Hanks et al.

The substrate specificities of kinases vary widely, and cannot be predicted a priori from the amino acid sequence. Some kinases have one or several protein substrates, while others may have hundreds. For example, the CK2 protein kinase phosphorylates more than 160 proteins and is involved in processes of transcription, signaling, proliferation and development (see Guerra et al., Electrophoresis, vol. 20, pp. 391-408, 1999). Applicants have not provided any evidence of what is the substrate of the polypeptide with SEQ ID NO: 2.

Another issue to consider when predicting protein function solely on the basis of sequence similarity is the fact that there are proteins with amino acid sequence which do not share sequence similarity with protein kinases, but do have a kinase function. One such protein is a BCR protein, which has only very little sequence homology to protein kinases, but is in fact a kinase as documented by experimental facts (see Maru et al., Cell, vol. 67, pp. 459-468, 1991; page 459, fourth and fifth paragraphs, Fig. 1, Fig. 2, Fig. 6).

Sequence search performed at the USPTO indicates that polypeptide with SEQ ID NO: 2 is 100% identical over 346 amino acids to a protein of SEQ ID NO: 2 (human sequence) and 93.7% identical over 346 amino acids to a protein of SEQ ID NO: 4 (rat sequence) from the publication number US20020103116A1 (Wei et al.), and 93.7% identical over 346 amino acids to a protein of 417 amino acids (SEQ ID NO: 2) from a Japanese patent No. JP2000060571-A (Mitsubishi Chemical Corp) (see sequence comparisons). Neither of these three proteins have been shown to be a protein kinase. Their amino acid sequences and functions are putative.

Sequence search was performed at the USPTO for amino acids 1-231 of SEQ ID NO: 2 (asserted kinase domain). The best two results were obtained for previously known (i.e., available before the priority date) sequences:

1) 98.8% identity over 231 amino acids to a sequence from Japanese patent No. JP2000060571-A (Mitsubishi Chemical Corp), which is a putative kinase (see sequence comparison),

2) 48.1% identity over 231 amino acids with an amino acid sequence of Xenopus laevis kinase (PIR accession number S71887, see sequence comparison).

These sequence comparisons do not unambiguously identify amino acids 1-231 of SEQ ID NO: 2 as a kinase domain.

To summarize, sequence comparisons presented by Applicants and the conclusion based on these sequence alignments regarding the function of polypeptide with SEQ ID NO: 2 were not found convincing, therefore the polypeptide with SEQ ID NO: 2 does not have a substantial utility. The polypeptide would have to be expressed, shown to be a kinase, then it's regulators, substrate or substrates would have to be identified, and only then one could proceed to define a potential role played by this polypeptide in certain disorders or diseases.

Applicants assert that the polypeptide of SEQ ID NO: 2 may be involved in regulation of receptor signal transmission, in modulation of entry of cells into mitosis, in modulation of cellular differentiation, in modulation of cell death or in regulation of cytoskeleton function, and may be used to diagnose disorders related to it's activity, such as grow-related disorders, regulation of metabolism, pain or brain disorders (see Facts, C), part c). In order for a polypeptide to be useful for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polypeptide and a disease or disorder. The assertion of protein function on the

basis of sequence similarity alone is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the presence of the claimed polypeptide and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polypeptide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polypeptide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotide or the encoded protein with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner*, 148 USPQ at 696. The disclosure therefore does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Since the polypeptide of SEQ ID NO: 2 does not have a specific and substantial utility, a polypeptide encoded by nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, or a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or a fragment of at least 15 contiguous amino acids of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 (as claimed in claim 4 a)-c)), also do not have specific or

substantial utility. Even if the function of the polypeptide of SEQ ID NO: 2 was known, it is unlikely that a fragment of 15 amino acids would have any of the protein's activity, or that a nucleic acid sequence 60% identical to a nucleic acid comprising SEQ ID NO: 1 or SEQ ID NO: 3 would encode any polypeptide at all. Therefore all of the polypeptides to which claim 4 is drawn lack specific and substantial utility, and so do the methods of using them (claims 9 and 10).

The claimed protein compound and methods of it's use are not supported by a substantial utility because no substantial utility has been established for the claimed subject matter. Similarly, the other listed and asserted utilities as summarized above or in the instant specification are neither substantial nor specific due to being generic in nature and applicable to a myriad of such compounds. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the protein compound such that another non-asserted utility would be well established for the compounds.

Applicant should explicitly identify a specific, substantial, and credible utility for the claimed invention and establish a probative relation between any evidence of record and the originally disclosed properties of the claimed invention.

19. Claims 9 and 10 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by a specific, substantial, and credible utility or a well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

Written Description

20. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) For the purpose of this rejection only the part of claim 9 drawn to a polypeptide of claim 4 will be considered. Claim 9 is drawn to a method for identifying a compound which modulates the activity of a polypeptide of claim 4, the method comprising contacting a cell expressing the polypeptide of claim 4 with a test compound and determining the effect of the compound on the activity of the polypeptide. Claim 10 is drawn to a method of modulating the activity of a polypeptide of claim 4 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide. Therefore, methods of claims 9 and 10 depends can be practiced only if the polypeptide of claim 4 has an established activity which can be monitored during the course of modulation with a given compound.

The polypeptide of claim 4 is an isolated polypeptide (referred to as a 32374 polypeptide) selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof,

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes

to a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof under stringent conditions,

c) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2, and

d) the amino acid sequence of SEQ ID NO: 2.

B) Adequate written description of the methods of claims 9 and 10 requires the following elements:

i) an isolated polypeptide or presence of a polypeptide in cells used in these methods,

ii) known activity of the polypeptide, including it's substrates,

iii) the ways to measure polypeptide activity. (The knowledge of substrates is not necessary in cell-based assays, as long as ways to measure protein's activity in the cells are known).

B) The specification asserts that the polypeptide of SEQ ID NO: 2 is a protein kinase based on limited sequence homologies with kinase-like protein domains (Fig. 3-12). However, Applicants did not isolate the protein and did not show that the expressed gene is translated into protein which is present in the cells. It is well known in the art that mRNA stability and the translation level of a gene are influenced by a complex array of factors and that the presence of mRNA in the cell does not mean that the protein encoded by that mRNA will be found in the cell (see Jacobson et al., Annu. Rev. Biochem., vol. 65, p. 693, 1996; especially pages 693-696 and 706, 707). Therefore, presence of the mRNA encoding polypeptide of SEQ ID NO: 2 is not sufficient to conclude that the polypeptide is present in the cells in which the mRNA encoding it is found.

Applicants did not show that the isolated protein has a protein kinase activity, and no substrates of the polypeptide were described. Therefore none of the elements necessary to practice the invention according to claims 9 and 10 are described in the specification.

Regarding a polypeptide encoded by nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, Applicants did not provide any evidence that any of such sequences would in fact encode polypeptides, and if they did, that the polypeptides would have the same activity as the polypeptide of SEQ ID NO: 2. Applicants did not provide any examples of naturally occurring allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or any evidence that such allelic variants would have the same activity as the polypeptide of SEQ ID NO: 2. Applicants did not describe any fragments of at least 15 contiguous amino acids of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 which would have the same activity as the polypeptide of SEQ ID NO: 2. Therefore the specification does not provide a description of how to practice the methods of claims 9 and 10 with the polypeptides of claim 4 a)-d).

Enablement

21. Claims 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP 2164.01(a) Undue Experimentation Factors

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

A) For the purpose of this rejection only the part of claim 9 drawn to a polypeptide of claim 4 will be considered. Claim 9 is drawn to a method for identifying a compound which modulates the activity of a polypeptide of claim 4, the method comprising contacting a cell expressing the polypeptide of claim 4 with a test compound and determining the effect of the compound on the activity of the polypeptide. Claim 10 is drawn to a method of modulating the activity of a polypeptide of claim 4 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide. Therefore, methods of claims 9 and 10 depends can be practiced only if the polypeptide of claim 4 has an established activity which can be monitored during the course of modulation with a given compound.

The polypeptide of claim 4 is an isolated polypeptide (referred to as a 32374 polypeptide) selected from the group consisting of:

a) a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof,

b) a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, or a complement thereof under stringent conditions,

c) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO: 2, and

d) the amino acid sequence of SEQ ID NO: 2.

B) Practice of the methods of claims 9 and 10 requires the following elements:

i) an isolated polypeptide or presence of a polypeptide in cells used in these methods,

ii) known activity of the polypeptide including it's substrates,

iii) the ways to measure polypeptide activity. (The knowledge of substrates is not necessary in cell-based assays, as long as ways to measure protein's activity in the cells are known).

Applicants' disclosure regarding polypeptide of SEQ ID NO: 2 has been presented in the chapter "Facts and Assertions" above, and will be only briefly summarized here. The specification asserts that the polypeptide of SEQ ID NO: 2 is a protein kinase based on limited sequence homologies with kinase-like protein domains (Fig. 3-12). However, Applicants did not isolate the protein and did not show that the expressed gene is translated into protein which is present in the cells. It is well known in the art that mRNA stability and the translation level of a gene are influenced by a complex array of factors and that the presence of mRNA in the cell does not mean that the protein encoded by that mRNA will be found in the cell (see Jacobson et al., Annu. Rev. Biochem., vol. 65, p. 693, 1996; especially pages 693-696 and 706, 707). Therefore, presence of the mRNA encoding polypeptide of SEQ ID NO: 2 is not sufficient to conclude that the polypeptide is present in the cells in which the mRNA encoding it is found.

Applicants did not show that the isolated protein has a protein kinase activity, and no substrates of the polypeptide were described. Therefore none of the elements necessary to practice the invention according to claims 9 and 10 are described in the specification.

Regarding a polypeptide encoded by nucleic acid molecule comprising a nucleotide sequence which is at least 60% identical to a nucleic acid comprising the nucleotide sequence of SEQ ID NO: 1 or SEQ ID NO: 3, Applicants did not provide any evidence that any of such sequences would in fact encode polypeptides, and if they did, that the polypeptides would have the same activity as the polypeptide of SEQ ID NO: 2. Applicants did not provide any examples of naturally occurring allelic variants of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2, or any evidence that such allelic variants would have the same activity as the polypeptide of SEQ ID NO: 2. Applicants did not describe any fragments of at least 15 contiguous amino acids of a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 which would have the same activity as the polypeptide of SEQ ID NO: 2. Therefore the specification does not provide a description of how to practice the methods of claims 9 and 10 with the polypeptides of claim 4 a)-c).

Nature of the invention

Nature of the invention requires that the polypeptide with SEQ ID NO: 2 be in an isolated form or present in the cells used in the methods and that activity of a polypeptide with SEQ ID NO: 2 or it's variants claimed in claim 4 a)-c) be known and that it is possible to detect such activity. Applicants did not describe an isolated polypeptide with SEQ ID NO: 2 or any of it's variants. Applicants did not provide any evidence that this polypeptide is present in the cells. Applicants did not provide a convincing evidence that the polypeptide of SEQ ID NO: 2 is indeed a kinase. Therefore the elements necessary to practice the claimed invention are not present in the specification.

The level of predictability in the art

Protein kinases are known in the art, and assays for determining their activity are known. However, Applicants did not show that the polypeptide of SEQ ID NO: 2 or it's variants claimed in claim 4 a)-c) have kinase activity. Sequence search performed at the USPTO indicates that polypeptide with SEQ ID NO: 2 is 100% identical over 346 amino acids to a protein of SEQ ID NO: 2 (human sequence) and 93.7% identical over 346 amino acids to a protein of SEQ ID NO: 4 (rat sequence) from the publication number US20020103116A1 (Wei et al.), and 93.7% identical over 346 amino acids to a protein of 417 amino acids from a Japanese patent No. JP2000060571-A (Mitsubishi Chemical Corp) (see sequence comparisons). Neither of these three proteins have been shown to be a protein kinase. Their amino acid sequences and functions are putative. Therefore the function of the polypeptide of SEQ ID NO: 2 cannot be ascertained on the basis of the sequence comparison alone.

Moreover, proteins with predicted activities do not always exhibit such activities. For example, Wilks et al. (Mol. Cell. Biol., vol. 11, pp. 2057-2065, 1991), describe a JAK1 protein of 1142 amino acids, which was found to be a putative kinase on the basis of the presence of conserved structural features of protein kinases, but it's function as a kinase could not be confirmed experimentally (page 2059, Results; page 2058, the last three paragraphs, continued on page 2058). The authors commented that the absence of kinase activity may be due to a missing co-factor. On the other hand, proteins with no clear amino acid sequence similarity to the kinase family may be kinases on the basis of activity determination. One such protein is a BCR protein, which has only very little sequence homology to protein kinases, but is in fact a kinase as documented by experimental facts (see Maru et al., Cell, vol. 67, pp. 459-468, 1991; page 459, fourth and fifth paragraphs, Fig. 1, Fig. 2, Fig. 6).

Therefore sole reliance on limited sequence homology for determination of protein function, especially in the case of kinases, may lead to erroneous conclusions.

The amount of direction provided by the inventor

The only guidance provided by Applicants regarding function of the polypeptide with SEQ ID NO: 2 concerns additional sequence comparisons with databases of structural motifs, for example, additional determination of the kinase domain presence can be made by searching a SMART database (page 14, lines 15-26), the protein kinase domain may be located by searching a PFAM database or ProDom database (page 23, lines 10-31; page24, lines 1-3). The Applicants did not provide guidance of how to determine whether any of the variants related to the polypeptide of SEQ ID NO: 2 and claimed in claim 4 a)-c) have a kinase activity.

The existence of working examples

Applicants did not provide any working examples of expression or purification of the polypeptide of SEQ ID NO: 2, or any examples of how to determine whether this polypeptide is present in the cells. There are no working examples of how to determine or measure the activity of the isolated polypeptide or the polypeptide present in the cells. There are no examples of any other polypeptides related to the polypeptide of SEQ ID NO: 2 and claimed in claim 4 a)-c).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Regarding the polypeptide of SEQ ID NO: 2, it would have to be expressed and purified, and the presence of the protein would have to be confirmed in the cells transformed with the expression vector or in cells harboring the mRNA encoding it. Type of activity exhibited by the protein would need to be determined, as well as the substrates. Even though the previous steps may be routine experimentation, confirmation of the polypeptide activity may not be, considering that

protein kinases are frequently activated by other protein kinases or small molecules present in the cell, therefore these activators would have to be found as well.

Regarding polypeptides of claim 4 a), one would have to determine which of the large number of nucleic acids with at least 60% sequence identity to nucleic acids comprising SEQ ID NO: 1 or SEQ ID NO: 3 encode polypeptides, and procede with the steps outlined for the polypeptide of SEQ ID NO: 2. Since the condition is only of 60% sequence identity (which includes non-consecutively identical sequences) to nucleic acids comprising SEQ ID NO: 1 and SEQ ID NO: 3, the number of possible sequences to consider is staggering.

Regarding polypeptides of claim 4 b), one would have to determine which of the large number of nucleic acids hybridizing under stringent conditions to nucleic acids molecules comprising SEQ ID NO: 1 and SEQ ID NO: 3 encode polypeptides, and procede with the steps outlined for the polypeptide of SEQ ID NO: 2. Since the condition is only hybridization under stringent conditions to nucleic acids comprising SEQ ID NO: 1 and SEQ ID NO: 3, the number of possible sequences to consider is very large.

Regarding polypeptides of claim 4 c), which are fragments of at least 15 contiguous amino acids of SEQ ID NO: 2, the number of such fragments is very large, and an activity (or lack thereof) would have to be determined separately.

Therefore, practice of the methods according to claims 9 and 10 requires a large amount of undue experimentation.

Due to the large amount of experimentation necessary to determine activity of the polypeptide of SEQ ID NO: 2 and it's variants, the nature of the invention, the level of predictability in the art, the lack of direction provided in the specification regarding determination of the activity of polypeptide of SEQ ID NO: 2 and it's variants, the absence of working examples

directed to determination of the activity of polypeptide of SEQ ID NO: 2 and it's variants, undue experimentation would be required of the skilled artisan to make and use the claimed invention.

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

23. Claims 9 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Wei et al. (US2002/0103116 A1).

Wei et al. teach a polypeptide with SEQ ID NO: 2 which is 100% identical to the polypeptide of SEQ ID NO: 2 of the present application (see sequence alignment). Wei et al. teach a nucleic acid molecule with SEQ ID NO: 3, which is 81.6% identical to the 2893 bp of SEQ ID NO: 1 and a nucleic acid molecule with SEQ ID NO: 1, which is 99.8% identical to the 1041 bp of SEQ ID NO: 3 (see sequence alignment). The polypeptide and it's variants can be used in drug screening assays, in cell-based or cell-free systems, or to identify compounds that modulate kinase activity of the protein ([0067]-[0069], [0073]-0074]). The polypeptides can be used to screen compounds which interact with the kinase, e.g., bind to the kinase ([0076]).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (703) 308-1119. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

April 21, 2003

Teresa Strzelecka, Ph. D.

Patent Examiner

Teresa Strzelecka
4/21/03